Clinical review

Fortnightly review

Treatment of the common cold

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The common cold is the most frequent illness managed in general practice. Despite a long search for a cure only potential treatments for the symptoms have been established. Colds afflict most adults two to four times a year and children four to eight times a year, and the resulting hours of absenteeism from work or school have enormous economic bearings. Several viruses can cause the common cold, but rhinoviruses are by far the most common. Studies evaluating various treatments for the common cold are divided into experimentally induced and naturally occurring colds. Treatments studied included symptomatic measures, pharmacological blockers, and specific antiviral agents, as well as drugs with yet unestablished mechanism of action. A systematic, evidence based assessment of this literature is imperative for rational selection of treatment—if any—for patients with a common cold.

Summary points

- Alleviation of symptoms remains the only proved way to treat the common cold. First generation antihistamines, anticholinergics, and α agonists effectively reduce rhinorrhea and sneezing, but have minimal effects on other symptoms. Antitussive agents are probably of minimal benefit
- Over-the-counter cold treatments are effective only in adults and adolescents
- Antiviral drugs such as interferon alfa-2b are effective only if taken before symptoms develop
- Zinc may reduce the duration and intensity of symptoms but a safe effective dose is not yet established
- Mast cell stabilisers have shown promising results but have not been evaluated in large trials
- Overuse of cold treatments by both doctors and patients is a major problem requiring education of both parties

Methods

I reviewed articles cited in Medline between 1966 and 1997 using the keywords common cold, treatment, therapy, and drug treatment. I selected well designed randomised, double blind, placebo controlled trials and authoritative review articles on specific topics in treatment of the common cold. Articles published within the past five years were selected rather than earlier articles when appropriate. Out of 334 articles retrieved, 49 articles were selected for this review.

Antihistamines

First generation antihistamines have achieved the most favourable results in both naturally occurring and experimentally induced common colds. Oral doxylamine succinate,[1] clemastine fumarate,[2] and chlorpheniramine maleate[3] significantly reduced rhinorrhoea, sneezing, and weight of nasal secretions but had minimal effects on other cold symptoms. The effective dose varied depending on the compound studied. Drowsiness—a common side effect—can actually help patients whose colds disturb their sleep if the drug is taken at bed time. Long acting antihistamines such as terfenadine that are used for allergic rhinitis are not as effective, probably because of their lack of anticholinergic activity.[4]

Anticholinergics

Intranasal ipratropium bromide spray significantly reduced nasal drainage and sneezing in studies of naturally occurring colds.[5–7] The optimum dose used in these studies was 84 µg (two sprays of a 0.06% solution in buffered saline solution) in each nostril three to four times daily. The main side effects included nasal dryness, occasional epistaxis, and headache. The duration of relief of rhinorrhoea was not well defined but thought to be over three hours. These data suggest that inhaled anticholinergics could be useful for the average cold.

α Adrenergic agonists

These substances are potent decongestants and have been long used for treating the common cold. Both oral and nasal forms proved effective in natural and experimental cold models.[8 9] These drugs are not without hazards, however, and prolonged use can lead to a rebound effect (rhinitis medicamentosa). Care needs to be taken in patients with hypertension because of the sympathomimetic effect of these drugs.

PRIVATE COLLECTION

Steam inhalation

Breathing in steam from a bowl or jug is widely believed to ease the soreness and discomfort of a cold. Nasal hyperthermia (42°-44°C) administered for natural or experimental common colds resulted in subjective improvement of symptoms and objective increased nasal patency in two studies from Israel and the United Kingdom.[10 11] Attempts to reproduce these findings in the United States were unsuccessful.[12 13] Possible explanations given for this discrepancy included variations in the technique of administering steam and different strains of viruses involved. It is a cheap and safe treatment for patients who find it helpful.

Mast cell stabilisers

Nedocromil and sodium cromoglycate administered intranasally or by inhalation have been shown to reduce the severity of naturally and experimentally induced rhinovirus upper respiratory tract infections.[14–15] These drugs prevent the release of chemical mediators in response to infection and down regulate the intracellular adhesion molecule type 1 (the receptor for rhinovirus) in the inflamed airway epithelium. However, they have no effect on the frequency of viral shedding or the serological response to infection. Even though the safety profile of these drugs is excellent, they have not yet been evaluated in large epidemiological studies.

Non-steroidal anti-inflammatory drugs

Aspirin as well as other non-steroidal anti-inflammatory drugs has been suggested to increase nasal symptoms and virus shedding and decrease serum neutralising antibody response in volunteers infected with rhinovirus.[16 17] More recently, the cyclo-oxygenase inhibitor naproxen was found to reduce headache, malaise, and cough without altering virus shedding or antibody responses in experimentally induced rhinovirus colds.[18]

Vitamin C

During the past three decades numerous studies have assessed the potential role of vitamin C in the treatment or prevention of common cold. In 1975 Chalmers reviewed the available literature and published a meta-analysis concluding that "the minor benefits of questionable validity are not worth the potential risk, no matter how small that might be." [19] A more recent analysis of the same review by Hemila pointed out several errors and suggested that vitamin C significantly decreases the duration of episodes and the severity of symptoms of the common cold by an average of 23%.[20] The best dose of vitamin C for the treatment of the common cold was not determined, but the maximal benefit was not thought to be obtained with 1 g/day of the vitamin.[21]

Glucocorticoids

Farr et al found that intranasal and systemic glucocorticoids were ineffective in preventing experimental rhinovirus infection, although nasal inflammation was transiently suppressed initially.[22] Another study found no therapeutic value for oral prednisone in experimental rhinovirus infections. Although it reduced kinin concentrations in nasal washes, mean viral titres were higher in the steroid group.[23]

Antibiotics

In a recent American survey 21% of all antibiotic prescriptions for adults by ambulatory care doctors were for upper respiratory tract infections.[24] Another survey found that 60% of patients seen in primary care for the common cold received a prescription for an antibiotic.[25] A conservative estimate of the annual cost of antibiotic prescribing for the common cold in the United States in 1994 was $37.5 million. Overuse of antibiotics was widespread across states and medical specialties. This is obviously an important factor in the increase of drug resistant bacteria.

A well designed study from Switzerland found co-amoxiclav was beneficial in only the 20% of patients with common cold whose nasopharyngeal secretions contained *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.[26] Nevertheless, attempting to apply these findings might increase the overuse of antibiotics. A reasonable alternative strategy would be to ask patients to return in a few days if their illness does not improve with treatment of the symptoms.

Zinc

Eight controlled trials on the use of zinc to treat the common cold have been published. Four of these showed a beneficial effect and four did not.[27 28] There are several plausible explanations for this discrepancy, including differences in the efficacy of the formulation or dose used and different viruses involved. Some formulations, such as zinc citrate, might render zinc ions inactive. Doses well above the minimal daily requirements are needed to attain a therapeutic benefit. Con-

cerns were also raised regarding the adequacy of the placebo used in some of these studies.[29]

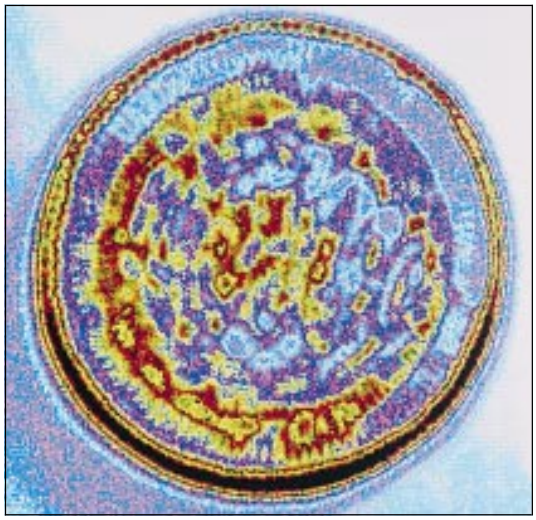
The exact mechanism through which zinc affects the common cold remains to be determined. One hypothesis is that zinc prevents rhinovirus from binding to the respiratory intracellular adhesion molecule type 1 on the epithelium, thus blocking viral entry into the cells.[30] Other hypotheses include inhibition of viral capsid protein synthesis, a membrane stabilising effect, inhibiting prostaglandin metabolites, and increasing production of interferon.

Interferon

Numerous studies have been conducted to evaluate the effect of intranasal interferon alfa on both natural and experimental colds. Results varied depending on the form of administration of interferon (spray *v* drops), dose given, frequency of administration, type of virus causing the illness, and whether interferon was given for prophylaxis or treatment. Interferon alfa-2b had some prophylactic efficacy in naturally occurring[31] and experimentally induced[32] rhinovirus colds when given before symptoms developed. The main side effect was local nasal irritation, dryness, and bleeding, which may be confused with nasal symptoms due to rhinovirus infection itself. Therefore, even though interferon is a powerful antiviral drug, it is not useful for treating colds.

Specific antiviral drugs

Influenza virus infections have been successfully treated with drugs such as amantadine, rimantadine, and zanamivir.[33] On the other hand, several studies using antiviral drugs against rhinovirus colds showed no appreciable clinical benefit,[34–35] even though in vitro studies gave promising results.[36] These drugs share a common mechanism of action, binding to specific hydrophobic pockets in the virion capsid and inhibiting virion attachment or uncoating.[37] The main obstacles for the development of effective antiviral drugs for the common cold include the wide variety of causative agents, mutant strains, and development of resistance. As with interferon, capsid binding drugs have no effect when given after symptoms have developed, and the local adverse effects of intranasal formulations may mask some of their beneficial effects.



ALFRED PASIEKA/SPL

A rhinovirus particle

Combination of agents

Numerous combinations of agents used for symptomatic or specific treatment of the common cold have been assessed and several other combinations remain to be evaluated. Combinations of α agonists with antihistamine and anticholinergics were not effective in relieving symptoms of the common cold in adults[9] or children,[38] while an α agonist combined with a non-steroidal anti-inflammatory drug resulted in a significant reduction in rhinorrhoea.[39] A critical review of clinical trials between 1950 and 1991 evaluating over-the-counter cold remedies demonstrated lack of effectiveness in preschool children, although adolescents and adults clearly benefited from certain combinations.[40] Patients should pay attention to the active ingredients of these combinations—for instance, most include a cough suppressive, which is probably not needed early on in the course of a cold.

Other agents

Aqueous iodine (2%) was successfully used to interrupt transmission of rhinovirus infection when applied to susceptible volunteers' fingers.[41] Although 2% aqueous iodine is cosmetically impractical, similar compounds with less staining properties might be appropriate, particularly in preventing transmission between family members. The expectorant guaifenesin had a marginal antitussive effect compared with placebo in young adults with natural colds but decreased sputum thickness and quantity.[42]

Discussion

Many of the studies reviewed here were conducted at the Common Cold Unit at Harvard Hospital in Salisbury and the Department of Internal Medicine at the University of Virginia Health Sciences Center in Charlottesville, Virginia, United States. Other excellent reviews on the subject have been published in the past 10 years.[43 44] In presenting these data, I decided not to perform a formal meta-analysis because the number of well designed published studies was very large, study designs were variable, and analysis of outcome was inconsistent. Many studies relied on subjective reporting of symptoms, making interpretation of the results difficult. The virus challenge model and the natural cold model both have their advantages and disadvantages.[45] Almost all experimentally induced studies used rhinovirus, which is epidemiologically sound but obviously provides an incomplete answer.

Methods of treating the common cold can be grouped into three categories: symptomatic measures such as anticholinergics; pharmacological blockers such as non-steroidal anti-inflammatory drugs; and antivirals such as interferon alfa-2b. An important obstacle to developing an effective treatment for the common cold is that viral replication in the upper respiratory tract peaks on the day symptoms start. Therefore, the key element in many of these studies was to start treatment within 24 hours of the onset of symptoms.

Much of the overuse of cold remedies can be ascribed to doctors' behaviour. A recent study in a family

practice teaching clinic estimated that 26% of patients seen for upper respiratory tract infections were given unnecessary drugs.[46] Doctors may mistakenly believe that patient satisfaction depends on receiving medicines, whereas taking time to educate patients about medicines and about when it is necessary to see a doctor would be more appropriate.[47] Two thirds of families possess several over-the-counter cold medications,[48] so the potential for toxicity, particularly in children, is considerable; in the United States 6.2% of all poisonings in children in 1996 were with cough and cold preparations.[49]

Several limitations to this review should be recognised. Firstly, any database search may miss certain articles because of different key words or changing headings. Secondly, some manufacturers may use unpublished data from company trials to support the use of their products. Thirdly, studies of naturally occurring common cold in different parts of the world may be evaluating different viruses, and studies of experimentally induced cold can assess only certain types of the many possible viral culprits.

In summary, treatment of symptoms remains the best available option for the common cold. Other promising agents include mast cell stabilisers, interferon alfa-2b, and zinc lozenges. Some combination of drugs might be the most logical answer, but cost and compliance remain significant practical problems.. Meanwhile, our responsibility is to avoid unnecessary and potentially harmful medications and to educate our patients when to seek medical advice and about the effectiveness, or lack of effectiveness, of the available treatments.

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